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The Relation of the Nervous System to Hæmophilia, Malarial Hæmaturia, Etc.

SECOND PAPER.

By C. H. Hughes, M. D., St. Louis.

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IN a paper read before this society, in November, 1884, after having shown from the testimony of all observation and the best accepted authority, that there is no constant capillary degeneration or microscopically discoverable blood change in this affection, I characterized it as an hereditary or congenital neuropathic affection of the sympathetic system, in the following introductory language:

We must look, therefore, to the sympathetic system, of which the most important is the vasomotor nerves and their nerve center, for an intelligible explanation of the phenomena of hemorraphilia, for under the healthy influence of the sympathetic fibers distributed to the arterial walls, these blood-vessels are kept in a state of normal tonic contraction and contractibility. The tonic contraction of the muscular coats of the arteries, even to the smallest arterioles, as they ramify and are lost in the minuter capillary system, divested of their external coat of connective tissue, and finally of their middle muscular coat, to the fusiform transformation of its fibers, is under nervous influence; and although the terminal branches of the sympathetic nerve, like the muscular coat of the arteriole, may no longer be traced in the capillaries, the capillary circulation is under the influence of the nervous system, not only through the *vis a tergo* of the heart's pulsating impulse, which, by multiform ramifications has been modified into a continuous flow, but by the reciprocal contraction with propulsive power of the arterial walls.

"The sympathetic nerves exert an influence on the muscular coats of the arteries similar to that of the cerebro-spinal nerves on the voluntary muscles" They cause contraction of these vessels, a diminished flow of blood through them, if stimulated, and relaxation and an increased flow through them if divided or lowered in vital tone.

If the flow of blood in a terminal arteriole is augmented through diminished contractile power and consequent dilation or dilatability of its walls, there will of course be a flushed capillary or distensible arteriole system, ready to burst or bleed profusely under slighter causes than

* Read before the St. Louis Medical Society, April 16, 1887.

would excite bleeding in a capillary system supplied by arterioles possessed of greater integrity.

In hæmophilia it is the impairment or comparative paresis of the habitual tonic contraction of the arterioles, the diminished tone of the circular fibers, which are the capillary sphincters as much so as the ordinary sphincters, which keep certain outlets of the body closed without voluntary effort, that is at fault. It is this weakened influence of the vasomotor power that permits certain other forms of hemorrhage of this kind, as of the stigmata. The suspended tonicity, as Dalton calls it, permits of the "action of an arrest."

Section of the sympathetic fibers of the carotid plexus, for example, which go to the distributions of this artery, causes relaxation of the blood-vessels, increased circulation, reddening of the venous blood, and increased salivation, while galvanization of their peripheral extremities precisely reverses results through excited contractility.

The effect of dividing the sympathetic, then, is to paralyze the muscular coats of arteries supplied by its filaments. "Owing to the paralysis, the arteries no longer offer their customary resistance to the blood-pressure coming from the heart. Their relaxation admits a larger quantity to the capillaries of the corresponding regions, and the causes are increased local circulation." Somewhere in the spinal cord and in the medulla oblongata, extending perhaps a little above (Schiff and others), nearly to the tubercula quadrigemina, but not to include them, or more widely scattered in the cerebro-spinal axis (Brown-Sequard, Vulpian and others), as shown by the influence of cross-sections upon vascular tonicity, is the nerve center which is probably chiefly at fault in the hemorrhagic diathesis, and this condition is amenable to such treatment as will impart tone and restore the vasomotor vigor which in this disease seems impaired.—*Vide Weekly Medical Review*, December 20th, 1881, pp. 517, 518.

Wickham Legg, in his article on the subject of Hæmophilia, in Quain's "Dictionary," speaks thus of the anatomical characteristics, or rather of their absence, in this disease: "No morbid appearances have yet been found with any constancy. The blood-vessels examined with the microscope have shown no change. The blood is apparently unaltered."

This I consider the true characteristic of hæmophilia. Neither the vessels nor the blood show a characteristic change, while in all other hemorrhages there is either a vascular wall or a blood change to account for the morbid phenomena, and this justifies us in locating the disease in the only organism which can justly be held accountable for the abnormal phenomenon. If the agents are not at fault we must look for the failure in the

principle, and hold the power which might prevent the hemorrhage—the arteriole walls and blood being healthy—accountable for the *lapsus morbi.*

If neither the structure of the capillary walls, dissevered from their nervous connection, nor the normal consistency of the blood is at fault, then we must find in the mechanism of nervous control the true *causa morbi;* and we need not, in order to understand this disease, here discuss the question whether there are vaso-dilators in the capillaries which overcome the weakened vaso-constrictors, or whether the power of contractility resides inherently in the arteriole walls without the necessity of nervous influence, as Poole, contrary to the popular view, maintains.

The fact is, in hæmophilia the normal contractile capacity and arteriole tonicity in the capillary walls is so impaired through evidently inherent conditions of the ganglionic centers, which preside over vasomotor inhibition, that blood exudes through the meshes of the capillary walls under circumstances of local irritation, or heart pressure or psychical influences which do not ordinarily cause this phenomenon in the majority of mankind.

The extraction of a tooth, the prick of the vaccinator's lance, the lancing of a gum or an abscess, the scratch of a pin, the bite of a leech, the cutting of the frænum linguæ, or the removal of a nasal polypus, a high altitude, gymnastic exercise, an over-stimulating meal with wine or brandy, which specially strain the capillary arteries and weaken vasomotor control, may start a fatal hemorrhage in a hæmophiliac whose age is an assurance that he has none of those characteristic arteriole degenerations common to later life, which dispose to sudden extravasations of blood.

The early period at which the first evidences of hæmophilia appear (often during the first year of life) precludes the reasonableness of the conjecture that the disease is due to undetected and undetectable vascular disease. Degenerative changes are not only seldom, if ever, found

at this age, but they would seem to be scarcely possible in a child not otherwise profoundly diseased. Hence, Legg's conjecture, that "it is most probably the vessels which are at fault, as in most of the other hemorrhagic diseases," about which we have the demonstrations of disease, is not justifiable. The fact in regard to hæmophilia appears to us to be just the opposite, viz., whereas we have in all other hemorrhagic diseases adequate pathological states of the blood or arteries to account for the existence of the hemorrhage, in this disease we detect, neither in the blood nor the arteriole wall, any sufficient cause. We must, therefore, look to impaired neural control of the arteriole caliber, through the vasomotor system, for the only sufficient explanation. Under this paresis of the sympathetic, so to speak, the arteriole caliber being without normal inhibitory neural control against dilation, the *vis a tergo* from the heart over-distends to the point of abnormal and often fatal exudation the arteriole capillary walls and the phenomena of bleeding becomes a possibility and a fact, without the necessity of evoking an unseen and undetectable disease of the coats of the vessels, or an impaired abnormal liquefaction of the blood, to account for it.

We should find no difficulty in seeing this matter in this light were we not too prone to look always to the direct seat of a morbid phenomenon for its sole causative explanation.

This was universal in the medical mind till the physiological neural phenomena of reflex transmission of symptoms became an accepted fact and had one of its earliest, if not its earliest, applications to disease in the knee pain symptom of hip-joint disease, followed up by the knee phenomena of antero-lateral and posterior spinal sclerosis, and in the reflected cardiac and utero-gangliopathias, and in the gastric and laryngeal symptoms of affections of the medulla and pons.

Neither the deficiency of fibrin theory, as accepted by Wood, Flint, Tanner, and others, nor the "delicate construction and vulnerability of the vessels and watery condition

of the blood" idea of Rokitansky are now tenable because they have been disproved, and the blood coagulates well after being drawn from these patients, especially in the early bleeding. It would not be strange, however, if, as the period of exhaustion after a prolonged and fatal bleeding is reached, the blood should be thinner in fibrin; and this may explain why in some cases the fibrin has been found deficient.

After the long continuance of the bleeding and consequent central nerve exhaustion it would not be strange to find the consistency of the blood altered as to the normal proportions of fibrin, and even of other essential ingredients, and it has so been found in some cases.

In death from lightning and other violent shock, and after section of the pneumogastric nerves, the blood has been found to have lost its power of coagulability.

On October 21st, 1884, while hæmophilia and purpura were under discussion before the Pathological Society of London, Dr. Acland showed some specimens taken from a case of hæmophilia in a boy aged seven, and from a case of purpura in a girl aged thirteen. In none of the organs or tissues of the former case which were examined were any lesions of the blood-vessels found such as have been described, either as regards their distribution or structure. No abnormal relation was found to exist between the blood supply and the size of the vessels; but the blood, which was examined after much hemorrhage had taken place, was found to be more watery than natural, and the white corpuscles were greatly in excess. The tissues round the wound from which the fatal hemorrhage took place were healthy.

At the same meeting, Dr. Wickham Legg said that he had read a paper before the society three years ago, stating that the examination of the tissues from a case of hæmophilia had revealed nothing differing from the natural state (*British Medical Journal*, p. 938, Vol. II., 1881). The specimens he now showed had been prepared and examined by Dr. Klein, who was unable to discover any

change, either in the vessels or tissues. The specimens were obtained from the body of a boy who died of epistaxis; diagnosis of hæmophilia in this case was very clear, and the the family history to some extent characteristic. The examination of the tissues had now been made in six cases; in four of these cases no change at all had been found; one in which changes were found was a case of extensive ichthyosis; the other was the case recorded by Dr. Percy Kidd, in which extensive changes in vessels were observed. Dr. Wickham Legg also showed specimens of joints from a case of hæmophilia. The condition of the joints had previously been observed in one case by Poncet, in one case by Sir William Jenner, and in one by himself; the same appearance was observed in all the cases. The first stage consisted in the extravasation of blood into the joint without any change in the structures of the joint. In the second stage, the synovial membrane was of a russet color, and there was slight erosion of the cartilage. In the third stage, the synovial membrane was deeply dyed and the cartilages extensively eroded and destroyed, so that the disease of the joint would seem to have its origin in the extravasation.

There is no question about the consequences of extravasation, but they are simply sequelæ; nor need we doubt the existence in exceptional cases of accompanying vascular disease or blood change. It would not be unreasonable to expect these at certain times and in certain stages, but the general absence of the local evidences of morbid change is the chief distinctive evidence to differentiate hæmophilia from purpura hæmorrhagica.

The *British Medical Journal*, while discussing the malady of Prince Leopold, thus candidly states the case, as follows: "We do not know what is the malformation or disease which predisposes to such an easy escape of blood from its proper channels. The chemical constitution of the blood has been thought by some to be at fault, the smaller blood-vessels by others; but no chemical or microscopical investigations that have been

conducted as yet have been anything but satisfactory, and, therefore, have been without result. One curious fact, however, has been elicited from various observations that have been made, and this is, that it is hereditary to a marked degree, and that it is transmitted along the male much oftener than along the female line."

Let us now again recur to the physiology of our subject. A little over a *century and a half* ago (1727) Pourfour du Petit, after cutting out the ophthalmic ganglion of a dog, observed an increased vascular turgescence to follow in the vessels of the eye. The later similar experiments of Claude Bernard, Brown-Sequard, and others on the cervical sympathetic have so fully confirmed the discovery of Petit that the phenomenon has become an accepted fact of modern physiology.

If the ischiatic nerve of a frog be divided the relaxation of the muscular coat of the arteries, on which the dilatation of their caliber by distention with blood depends appears to be an effect of a section of special vaso-constrictors, derived from the sympathetic, bound up in the ischiatic trunk, and not of fibrils derived from the spinal cord. Thus T. Wharton Jones, in a paper on "The State of the Blood and the Blood-vessels in Inflammation," showed, in a communication to the Royal Medical and Chirurgical Society, in May, 1883, in the "Medico-Chirurgical Transactions," Vol. XXXV., and "Guy's Hospital Reports," October, 1853, that if we lay open the lower part of the vertebral canal of a frog, and remove the roots of the ischiatic nerves with the corresponding portion of the spinal cord, so that all sensation, voluntary motion, and spinal reflex action in the posterior extremeties are abolished, the walls of the arteries are nevertheless seen, on examination of the webs under the microscope, to retain their contractility; nay, they appear even more disposed to become contracted, so as to keep up greater than ordinary constriction of the caliber of these vessels.

When, now, the trunk itself of the ischiatic nerve in

the thigh, which comprises not only the spinal fibrils, sensitive and motor, the roots of which were with the corresponding portion of the spinal cord destroyed, *but also fibrils from the sympathetic nerve in the pelvis as yet uninjured*, was divided on one side, the skin of the extremity subjected to this part of the experiment was seen by the naked eye to become redder from general vascular fulness than that of the opposite extremity, and on microscopical examination of the web the arteries were observed to be relaxed and dilated by distention with full and rapid streams of blood injecting the capillaries and venous radicles. In the web of the opposite extremity, in which the trunk of the ischiatic nerve in the thigh was left uninjured, the arteries were, on the contrary, seen much constricted, some even to closure. This remarkable fact would appear to indicate something like the operation of inhibitory nervous influence having been arrested by the destruction of the spinal roots of the ischiatic nerve and the corresponding portion of the spinal cord whence they originate, leaving the vaso-constrictors derived from the sympathetic in uncontrolled action.

The electric irritation of the chorda tympani nerve gives a phenomenon different from that which immediately follows the peripheral stimulation of other nerves presiding over vascular and glandular supply. In this experiment, first performed by Claude Bernard, when the nerve is excited by electricity, the arteriole walls of the blood-vessels dilate, the submaxillary secretion is accelerated and profuse. This is exceptional and may be explained on the hypothesis of speedier exhaustion of central inhibition than we see elsewhere.

The effect of a smart blow on the skin or of a sudden scald is something like it, but here there is more or less of capillary destruction. The action of a blister in its primary stimulation and final exhaustion of vasomotor tonicity, followed by relaxation and exudation of serum, is a therapeutic illustration.

But whatever view we take of the *modus operandi* of

peripheral irritation on the capillary circulation, the fact remains that the movements of the blood current are presided over by a central nervous system mainly located in the sympathetic chain of ganglia and its fibrils, and that whether there be vaso-dilator as well as vaso-constrictor fibers, or only vaso-constrictor fibers, and probably inhibitory fibrils going beyond the vasomotor ganglia, and if arterioles permit the blood to extrude through their walls without our being able to detect appreciable structural disease in them or in the blood current, the condition that permits this is disease, and this disease can only be in the nervous system. Since the publication of my first paper on the subject, and since this paper was written (May, 1886), though it is only just now given to the medical press, papers have appeared accepting this view in part as the proper explanatory view of its pathology; among them a paper by Thomas Oliver, M. R. C. P., in the London *Lancet.*

Whatever other pathological co-existences may be found, neuropathic or otherwise, in any case, I believe the essential pathology of this disease is in defective central action on the part of the vasomotor center, a view which Oliver accepts only in part. A defective blood condition as to its fibrinous constituents and coagulability may precede or follow hæmophilia; but this is certainly not an invariable or even a common causative condition.

What is true of hæmorrhaphilia is true, in part at least, and in the chief part we think, of hæmorrhagic malarial fever, of purpura hæmorrhagica and certain erythemas, the two latter, according to E. Wagner, being closely related.

In simple purpura and urticaria, hemorrhage takes place in the skin only. In malarial hæmaturia the sanguineous exudate is chiefly into the stroma of the kidneys, the malpighian tufts, and the tubuli uriniferi; but, wherever it is, though the more remote cause be malarial

toxæmia, the immediate is in the lost vasomotor control that allows arterial dilatations and permits of the fatal pressure of passive congestion and sanguinuric excretion.

Dr. W. Allen Jamieson, lecturer on Diseases of the Skin, in the Edinburgh School of Medicine, in a review discussion of purpura and erythema in the *Edinburgh Medical Journal* for March, expresses the common feeling on these subjects when he asks, Why in certain cases of tubercular erythema hemorrhage occurs so constantly, so quickly, and so severely? and answers, that it cannot be explained by the youth of the patients, nor from their anæmic conditions; and concludes that, some hitherto unknown cause exists, as in hæmorrhagic smallpox. That hitherto unexplained cause is in the paralysis of vaso-motor control.

A thoughtful and observant writer in the Texas *Courier-Record of Medicine*, Dr. Jas. A. Abney, of Tufkin, Texas, writing on malarial hæmaturia, strikes the true pathology in his second proposition, that, following the pre-existing toxæmia, "the resulting pathological condition is one of vasomotor depression, with consequent vascular expansion."

A survey of other fields of clinical observation, for which we have here neither time nor space, serves to confirm the conviction enunciated by us years ago, that the neural pathology is destined to reign pre-eminent in medical thought.